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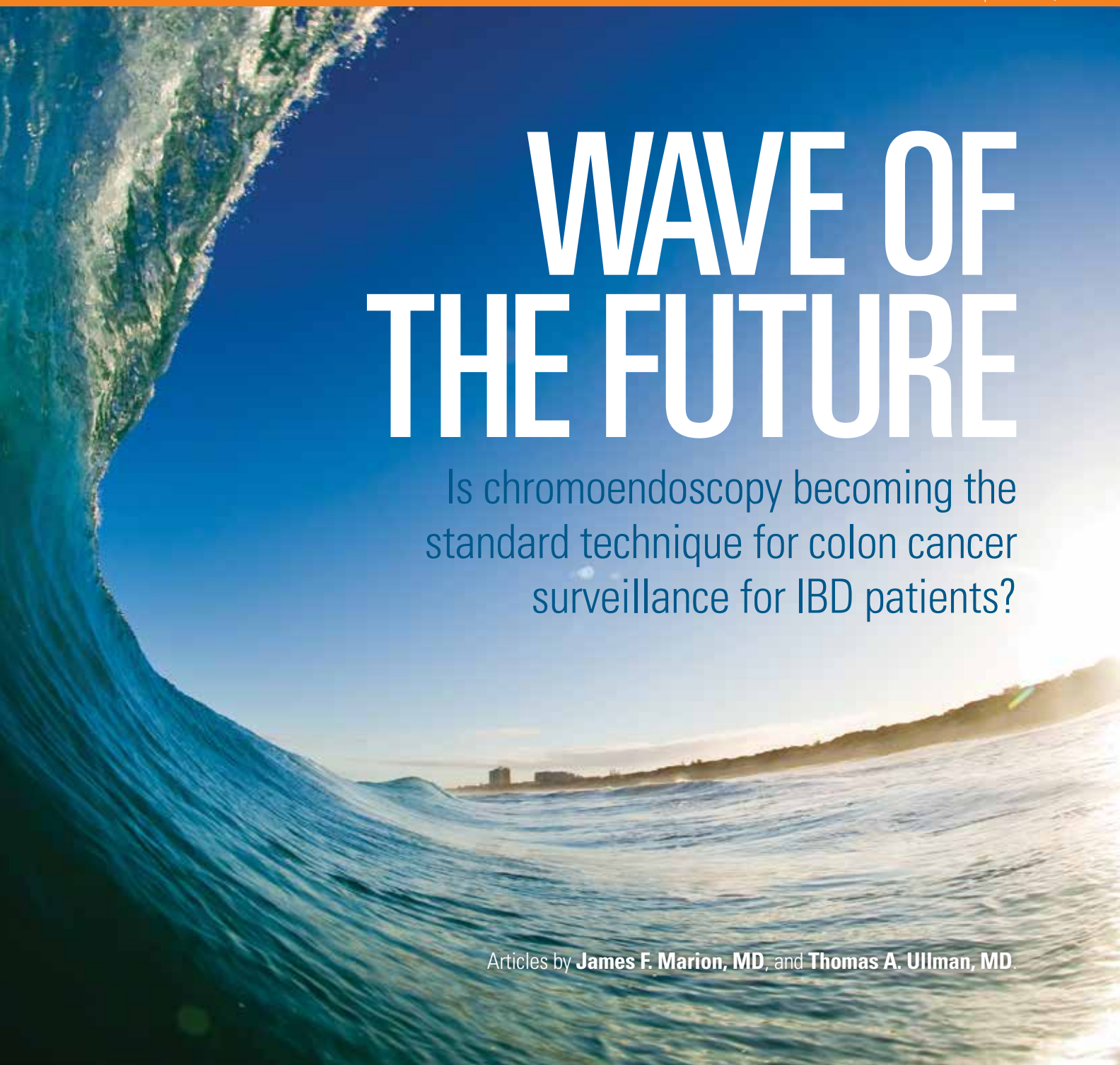

WAVE OF THE FUTURE

Is chromoendoscopy becoming the standard technique for colon cancer surveillance for IBD patients?

Articles by **James F. Marion, MD**, and **Thomas A. Ullman, MD**.

AGA Perspectives

In this issue

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AGA INSTITUTE

Note From the Editor

In this issue of *AGA Perspectives* we address a number of rapidly evolving areas of GI practice. In our opening point-counterpoint debate, Drs. Marion and Ullman weigh in on the important issue of chromoendoscopy in IBD surveillance. This is especially important with the recently published and debated SCENIC guidelines earlier this year.

Dr. Seth Gross provides a perspective on the wide variety of new tools for enhanced detection of colon polyps that have recently become available leading to the dilemma of which ones, if any, to adopt into clinical practice.

There continues to be confusion on treatment strategies for *H. pylori* infection, which is addressed by Dr. David Graham. This is especially important given the continued use of suboptimal treatment regimens for *H. pylori*. Updates are also provided on the conundrum of treatment of hepatitis C either before or after liver transplantation as well as new evolving approaches to celiac disease beyond just a gluten-free diet.

AGA Perspectives is also a chance to update the membership on recent AGA activities and priorities. Dr. Ziad Gellad, chair of the AGA Quality Measures Committee, updates us on quality measures for clinical practice. In this issue, we are introduced to our new president, Dr. Michael Camilleri, and hear from Dr. Michael Kochman about the recently completely AGA Tech Summit.

Gary W. Falk, MD, MS, AGAF
EDITOR
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WAVE
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Is chromoendoscopy becoming the standard technique for colon cancer surveillance for IBD patients?

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CHROMOENDOSCOPY: THIS IS WHAT PROGRESS LOOKS LIKE

James F. Marion, MD

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Most questions I hear from patients with longstanding colitis having surveillance for colon cancer remain pertinent and practical: Do I have dysplasia? Where was it? What did you do about it? Will I get cancer? Do I need surgery? How often do I need to have a colonoscopy? The questions from gastroenterologists are similarly pragmatic: Do I still need to do random biopsies? The colon looks so normal. Do I still need to scope them as often? Our current guidelines leave many of these questions unaddressed.[1]

The SCENIC consensus group is correct; our guidelines and recommendations for detecting and managing dysplasia in colitis are based upon an outdated literature using outmoded detection techniques.[2]

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CHROMOENDOSCOPY: STILL NOT READY FOR PRIME TIME

Thomas A. Ullman, MD

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The backbone of colorectal cancer prevention in inflammatory bowel disease (IBD), as in sporadic colorectal cancer prevention, has been colonoscopic screening and surveillance. The purpose of colonoscopic surveillance in IBD is to identify dysplasia and intervene to prevent its progression.

Early in the history of dysplasia surveillance in IBD, intervention meant colectomy following the detection of dysplasia and continued periodic examinations for those who were dysplasia-free or those who felt that the risks of cancer following dysplasia were low enough to avoid the risks of colectomy. With the demonstration of the relative safety of continued surveillance following polypectomy[1,2] and the understanding that most

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For years, we have trudged like Marley's ghost "captive, bound and double-ironed" to the long, heavy chains of an unwieldy and antiquated random biopsy evidence base despite strong evidence over the last decade showing chromoendoscopy with targeted examination to be a more effective means for detecting dysplasia when it develops.[3,4] Investigators continue to ignore the robust, prospective evidence base for chromoendoscopy and continue to add weak, retrospective links to the random biopsy rationale chain.[5] Patients and gastroenterologists are confused, and we have only ourselves to blame.

The controversy surrounding chromoendoscopy and SCENIC is welcome and necessary, but long overdue, chapter in the progress toward better detection for these patients. One must revisit the transition from contrast radiography, specifically barium enema, to colonoscopy for polyps or colorectal cancer screening to find a similarly messy, contentious but necessary process.[6] The emergence of colonoscopy as the procedure of choice was not based on consensus as much as an appreciation of the practical advantages of reliably identifying a polyp and plucking it out. Still, it has been a decades-long and agonizing defeat for our radiologic colleagues who have continued this battle under the new flag of CT colography sometimes resorting to aromatherapy and soothing music to distract us from the impracticality of the method.[7,8] The SCENIC group aimed for consensus and practicality.

The SCENIC recommendations should encourage gastroenterologists to more clearly characterize dysplasia at screening in this population and be a springboard for further study. What else has improved aside from our scope resolution since Blackstone's work in the 1980's?[9] We have developed a far more sophisticated set of tools to crack the code of cancer in IBD. We can track dysplasia more closely and apply our best translational, genomic, microbiomic and digital resources to capture the full natural history, from stem cells to metastases, of dysplasia in IBD.

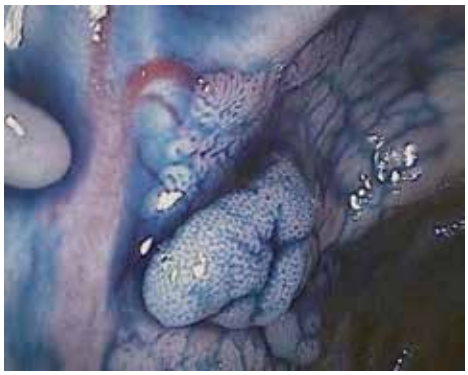

IMAGE COURTESY OF PENTAX MEDICAL

Image of a colitis patient with inflammatory polyps and dysplasia detected through chromoendoscopy.

Advances in clinical electronic data collection and medical record mining greatly increase our ability to collaborate across medical centers, and even across continents. Finally, each year, we are graduating a new class of fellows with endoscopic skills far more sophisticated than mine were upon graduation to meet the endoscopic challenges these newly identified dysplasias will create. Continuing to randomly poke around our patient's colonic mucosa will get us nowhere.

We have an evidence base and consensus that chromo finds more dysplasia than any other technique we are doing now, but is detecting dysplasia enough?[10-14] Not all dysplasias carry the same prognosis. The majority of the dysplasias detected in these referral populations were manageable endoscopically. The question of long-term management of these patients remains a glaring gap in the SCENIC recommendations. Avoiding cancer remains an admirable goal, but other goals such as protecting patients from too onerous surveillance schedules, unnecessary colectomies or even surprises after colectomy, must be accomplished as well. The Barrett's model, using endoscopic resection and ablation to preserve the esophagus, may be a good model to replicate.

Now we have to roll up our sleeves and map the natural history, determine which dysplasias in which patients can become dangerous and communicate this in a clear and practical fashion to our patients. We must capitalize on the advantages of this technique to clarify our understanding of the natural history of dysplasia in our patients to the point where we can stratify them safely according to their risk. Our target is polyps that are smaller, flatter, rarer and less likely to result in a catastrophic outcome for most patients.[15] We need to reach across the aisle to our colleagues in the breast and prostate cancer prevention communities as they formulate their guideline recommendations. This will require multi-center collaboration and funding to execute a prospective study of the practical efficacy of these techniques. Dysplasia detection rates are not enough, a strategy to identify those patients truly at risk and improve outcomes must be the goal.

The SCENIC group was silent on several practical issues such as random biopsy. The same prospective, endoscopic trials that demonstrated the superiority of chromoendoscopy also showed the startling futility of random biopsy to detect dysplasia. This has led some to recommend abandoning the practice altogether and adopt targeted techniques.[16] Endoscopy centers of excellence compare adenoma detection rates among endoscopists and we must take the same results-oriented approach to our patients when we are doing chromoendoscopy. To completely

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International Consensus Statement on Surveillance and Management of Dysplasia In Inflammatory Bowel Disease

In March 2015, AGA and ASGE issued updated recommendations for the surveillance and management of dysplasia in patients with inflammatory bowel disease based on the "Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC)."

Patients with ulcerative colitis or Crohn's colitis have an increased risk of colorectal cancer. Most cases are believed to arise from dysplasia, and surveillance colonoscopy therefore is recommended to detect dysplasia.

With the advent of video endoscopy and newer endoscopic technologies, investigators now report that most dysplasia discovered in patients with IBD is visible. Such a paradigm shift may have important implications for the surveillance and management of dysplasia.

The evolving evidence regarding newer endoscopic methods to detect dysplasia has resulted in variation among guideline recommendations from organizations around the world.

To help direct future practice, the AGA and ASGE consensus statement includes the following statements for surveillance and detection:

- **Statement 1:** When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition.
- **Statement 2:** When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy.
- **Statement 3:** When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy.
- **Statement 4:** When performing surveillance with standard-definition colonoscopy, narrow-band imaging (NBI) is not suggested in place of white-light colonoscopy.
- **Statement 5:** When performing surveillance with high-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colonoscopy.
- **Statement 6:** When performing surveillance with image-enhanced high-definition colonoscopy, narrow-band imaging is not suggested in place of chromoendoscopy.

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CHROMOENDOSCOPY: STILL NOT READY FOR PRIME TIME

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dysplasia in surveillance programs is visible,[3,4] continued surveillance following polypectomy has become the norm, and a number of unneeded colectomies has been averted. The focus of surveillance shifted from taking multiple non-targeted biopsies to a strategy familiar to all endoscopists of polyp identification and removal. The goal, then, in improving surveillance through technologic advance has thus become improving polyp detection.

But while the focus on lesion identification has come to the fore, questions regarding the clinical utility of endoscopic advances must always remain the same, whether in IBD surveillance or in any endoscopic advance: what are the true benefits to the new technology?

The best of the newer methods of colonoscopic advances in IBD, at least in cross-sectional studies, has been the application of diluted methylene blue or indigo carmine to the colonic mucosal surface with careful inspection of the colon to better detect previously "invisible" flat dysplasia, techniques commonly referred to as chromoendoscopy. The promise of chromoendoscopy is outstanding and results have been very encouraging; greater detection of dysplasia on both a per-lesion and per-patient basis has been demonstrated in multiple studies from multiple centers.[5-8] Every one of these studies, however, has been a cross-sectional process evaluation, in which the number of detected lesions using chromoendoscopy has been compared to the number of detected lesions using conventional white-light colonoscopy (or in one study the number of patients with detected lesions). No longitudinal studies have been reported in the peer-review literature. And so no comparisons to conventional white-light examinations have ever been performed for any clinically meaningful outcome. There are no studies showing a colorectal cancer mortality benefit; none with a morbidity benefit; no evidence to show a decreased colectomy rate; and no studies

> There is no peer-reviewed evidence whatsoever that has demonstrated any benefit that accrues to IBD patients undergoing chromoendoscopic examinations compared to white light examinations.

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Investigators continue to ignore the robust, prospective evidence base for chromoendoscopy.

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free ourselves from the chains of our outdated evidence base, we must build the foundation for a new one and SCENIC is the cornerstone.

This latest chapter in our evolving management of dysplasia in colitis is being encouraged and watched by our patients.[17] Patient advocacy has become the norm in our modern medical culture, but in this instance has been met with some resistance by the gastroenterology community. Patients with IBD bear the brunt of our lack of understanding of these diseases and the resultant controversies. Their practical concerns bring a refreshing perspective to the table. Further, our current surveillance approach has performed poorly when put to the same level of scrutiny as chromoendoscopy and our patients pick up on our disillusionment.[18,19] We need to be clear with our patients about what chromoendoscopy in this setting can and cannot do. We have a new and effective technique to answer many of our patients (and our own) questions about what dysplasia in colitis might portend. Now we have to get to work to establish long-term strategies. There is still work to be done to justify our surveillance strategies for the gastroenterology community, and most importantly, our patients. This work will involve diluting up some blue dye, stepping on the foot pedal, covering the mucosa with dye and finding a dysplasia in your patient when it's there, or not when it's not. Next, tracking the incidence of dysplasia in this population of patients over time with the goal of being able to predict the patient's risk of developing colon cancer.

This is what progress looks like. ■

Dr. Marion has no conflicts to disclose.

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demonstrating cost savings or decreased patient burden. In fact, there is no peer-reviewed evidence whatsoever that has demonstrated any benefit that accrues to patients undergoing chromoendoscopic examinations compared to white-light examinations. None.

Why not? Is it possible that chromoendoscopic IBD surveillance saves lives, decreases costs, and limits the time and burden on patients compared to conventional white-light examinations? Sure. But these are the missing studies. We should keep in mind that while benefits with improved dysplasia detection are possible, it's also possible that the improved dysplasia detection demonstrated in the cross-sectional studies is limited to better viewing of small and clinically less important lesions that are not likely to be missed on the next surveillance examination prior to their becoming clinically important. The possibility and extent of such lead-time bias has never been investigated in IBD and not particularly well discussed in the chromoendoscopic literature. The benefit of chromoendoscopy, therefore, as of this writing is just theoretical as no benefits have been demonstrated.

Recently, the SCENIC group (in which I was a participant) published its consensus statements in multiple journals.[9,10] If fully adopted, the SCENIC recommendations will mandate that our fellow gastroenterologists be obliged to learn chromoendoscopic techniques and purchase high-definition scopes, high-definition processors and high-definition monitors to be in compliance. This was done in spite of the complete absence of longitudinal data supporting an outcome benefit or clinical utility to chromoendoscopy; as of this writing chromoendoscopy is a faith-based initiative. While there isn't great evidence to support conventional white-light based surveillance practices either, I believe that gastroenterologists should continue to feel free

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to adopt or not to adopt chromoendoscopy as their go-to method of performing surveillance. One day, soon I hope, investigators will perform scientifically rigorous, longitudinal studies evaluating the benefits of chromoendoscopy, evaluating true patient-oriented outcomes like cancer morbidity or mortality, scope intervals or costs, all feasible if performed in a multicentered fashion. Then we might come to understand the true value of chromoendoscopy. Until then, chromoendoscopy looks great and shows promise, but conventional white-light surveillance for IBD patients, as recommended in the AGA Guidelines, is still king.[11] ■

Dr. Ullman receives research support from Genetech and also serves on the Crohn's and Colitis Foundation of America government affairs committee.

Chromoendoscopy is a faith-based initiative.

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New Colon Technologi

Seth A. Gross, MD

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Dr. Gross is a speaker for MEDIVATORS Inc.

Colonoscopy has been shown to detect both adenomatous polyps and colon cancer. However, studies have shown colon adenomas and colon cancer have been missed despite having colonoscopy. To reduce the miss rates during colonoscopy, rigorous quality metrics have been developed. Recently a multi-society quality guideline was released stressing the importance of key metrics: bowel preparation, adenoma detection rate (ADR), cecal intubation and withdrawal time. The ADR benchmarks have increased to 30 percent for men and 20 percent for women. A split-dose bowel preparation is recommended as well as a withdrawal time of no less than 6 minutes.[1] In the last of couple of years, there has also been a parallel improvement in equipment to potentially improve inspection of the colon with the goal of reducing the miss rate of adenomatous polyps.

Currently, high-definition white light (HDWL) colonoscopy is a common feature in a new colonoscope, but has demonstrated a marginal benefit for improving ADR. Digital chromoendoscopy (NBI, iScan, FICE) have not shown a higher ADR when compared to HDWL. Today, newer technologies can be subdivided into either "optical enhancement" or "mechanical enhancement." These enhancements aim to get better surface visualization of the proximal area of the colonic folds and colon blind spots, such as flexures. The standard view of a colonoscope can range anywhere from 140 to 180 degrees. Full spectrum endoscopy (FUSE) has a center image of 160 degrees with

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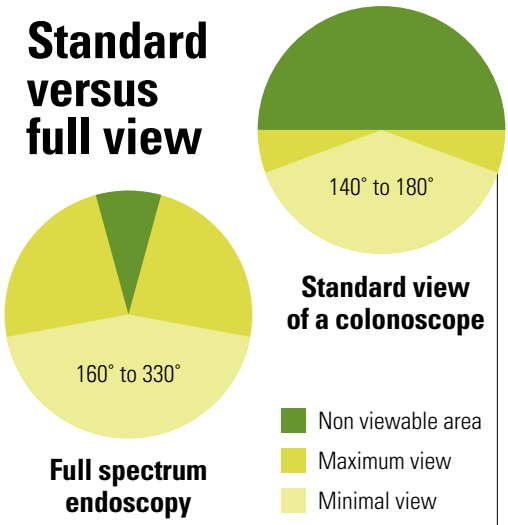

two additional side cameras increasing the field of view to 330 degrees. A single randomized study showed a significant ADR increase of 71 percent along with a decreased adenoma miss rate 7 percent (FUSE) versus 41 percent (standard forward view).[2] However, this is only a single study and more studies are needed to confirm this dramatic ADR advantage.

Several years ago the third-eye retroscope was a camera-based catheter, which went down the working channel of the scope and would come out retroflexed to view proximal folds. The device has been redesigned in the form of a panoramic cap, which has two cameras on each side of the cap. When snapped onto the tip of the scope the field of view increases to about 330 degrees.

Newer technologies can be subdivided into either "optical enhancement" or "mechanical enhancement."

Mechanical colonoscope enhancements are either single-use caps or a permanently integrated balloon, which is reusable. Endocuff (EC) is a single-use cap with soft fingerlike projection allowing for temporary gripping of colonic folds revealing the proximal side. A recent study showed a 14.7 percent increase in ADR compared to traditional optical colonoscopy.[3] EndoRing (ER) is a disposable cap with circular rings, and when engaged with colonic fold it can cause mechanical shortening to stretch the colon and to better visualize colonic folds. Randomized study compared ER to standard colonoscopy and demonstrated a reduction in the ADR miss rate compared to standard colonoscopy. Another form of mechanical enhancement is the G-EYE, which is available outside the U.S. The G-EYE is an integrated balloon colonoscopy, which has an inflated balloon at the tip used during withdrawal. The balloon stretches the colon allowing for flattening of colonic folds. A prospective randomized control trial showed a significant reduction in ADR miss rate for the G-EYE, 7.5 percent, compared to 44 percent with standard colonoscopy.[4]

Quality indicators in colonoscopy have been established and are here to stay. The formula to achieve a high-quality colonoscopy is composed of endoscopist's technique with quality equipment (HDWL). The technological advances in this space are changing the face of colonoscopy as we know it. The routine use of either optical or mechanical enhancements will be better defined as more scientific data is published.

There are several unanswered questions:

- Is optical or mechanical colonoscopy enhancement a need for every endoscopist?
- Should these advances be used only by those with a below benchmark ADR?
- Which is a better, optical or mechanical improvement?
- Do the cost implications of these technologies lead to improved outcomes?

There is continued emphasis on improving an endoscopist's batting average, which is their ADR. After the endoscopist has exhausted correcting adjustable factors, such as bowel preparation, withdrawal time and inspection technique, but is still not achieving high-quality exams, the hype of new colonoscopy technology may ultimately be helpful. ■

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A *GREAT* DAY FOR CELIAC DISEASE

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Dr. Kupfer has no conflicts to disclose.

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Celiac disease has long been an outlier in the panoply of intestinal diseases. While not on par with IBS, it is significantly more common than IBD or eosinophilic disorders. While patients are not often hospitalized or in the operating room due to celiac disease, the attributed mortality is increased and burden of treatment appears to be higher than any other common luminal disease. Enteropathy is a hallmark of disease, yet, unlike ulcerative colitis, evidence does not support a strong relationship between persistent mucosal inflammation with symptoms or long-term outcomes.

These issues are all vexing but perhaps most relevant to patients and clinicians is the fact that despite the prevalence, morbidity, burden and overall highly unmet medical need, the field of celiac therapeutics has been nascent. To date, only 11 randomized controlled therapeutic trials have been published in the last 20 years, including four with larazotide acetate, one with ALV003, one with ANPEP, two with probiotics, one with rifaxamin, one with hookworm inoculation and one with pancreatic enzymes. Therapeutic development for celiac disease is hardly a thriving field, and there are multiple reasons for this current state of affairs. The major historical obstacles to drug development have been the misperceptions that celiac disease is rare and mild, and that the gluten-free diet is a near optimal therapy. Over the last decade, these premises have fallen under robust scientific scrutiny; yet one major hurdle remained, a regulatory path to approval.

On March 31, 2015, therapeutic development in celiac disease took a major step forward with a full day devoted to advancing celiac disease therapeutics during the third Gastroenterology Regulatory Endpoints and Advancement of Therapeutics (GREAT 3) workshop sponsored by the FDA Center for Drug Evaluation and Research and co-sponsored by the American Gastroenterological Association. The meeting covered defining target populations for pharmacologic therapies, defining clinical benefit in celiac disease clinical trials, and measuring clinical benefit in celiac clinical trials to support marketing approval.

In March, 2015, FDA held the GREAT meeting to discuss issues related to the selection of endpoints and clinical outcome measures appropriate for drug development in celiac disease and IBD.

The workshop kicked off with an overview of current management of celiac disease and identification of target populations in adults and pediatrics by Joseph A. Murray, MD, Mayo Clinic, Rochester, MN, and Alessio Fasano, MD, Massachusetts General Hospital, Boston. Both speakers emphasized that the gluten-free diet, while effective, is hardly an optimal therapy. Dr. Murray noted that not all adult patients experience complete symptom relief nor complete mucosal healing, which can have consequences for quality of life and long-term complications. In pediatric populations, Dr. Fasano emphasized adherence challenges of children and adolescents, and the need for alternative therapeutic options along the age continuum. Among speakers and panelists, there was clear consensus that initial focus of drug trials should be symptomatic celiac patients with evidence of persistent mucosal damage. Additional populations to consider include screen-detected patients belonging to higher risk groups (e.g., type 1 diabetes or family members) whose

symptoms may be less severe but face unique challenges in adherence to the gluten-free diet.

The second session expanded on these themes by defining clinical benefit from the perspective of patients, adult and pediatric gastroenterologists, and FDA. Alice Bast, the patient representative, shared her personal challenges living with celiac disease and explained how adjunctive therapies are needed and desired by the celiac community. Sheila E. Crowe, MD, University of California, San Diego, and Ivor Hill, MD, Nationwide Children's Hospital, Columbus, OH, presented assessments of clinical benefit as adult and pediatric gastroenterologists. Dr. Crowe underscored that patients want to live normal lives and how drug therapies could help achieve this primary goal. Dr. Hill presented specific scenarios and expected clinical benefit in children. Finally, Jessica Lee, MD, medical team leader, FDA Division of Gastroenterology and Inborn Errors Products, outlined the FDA's perspective on clinical benefit emphasizing use of patient reported outcomes and/or objective measures of disease activity. Speakers and panelists discussed a myriad of topics including the role of quality of life measurements in trials, challenges in dietary adherence assessments, and similarities between pediatric and adult celiac disease.

The final session addressed the difficult issue of how to best measure clinical benefit in pivotal clinical trials and covered patient-reported outcomes, histologic assessment and serologic tests. After a review of patient-reported outcomes by Elektra Papadopoulos, MD, of FDA, Benjamin Lebwohl, MD, Columbia University Department of Medicine, New York, NY, presented compelling data that quantitative histology should be used as the primary endpoint in gluten challenge studies, as the kinetics of gluten-induced inflammation are well known. Conversely, the timing and clinical significance of induced reduction in enteropathy are very poorly understood and, at this point, should not serve as a sole primary endpoint in a pivotal trial. There appeared to be good consensus that histology should be evaluated in trials of incompletely controlled celiac disease, but this could serve as either a co-primary or safety endpoint. The final sessions discussed the role of celiac serologic testing in clinical trials. It was noted by Julia Lathrop of the FDA Center for Devices and Radiologic Health that all celiac serologies are currently approved only as an 'aid in diagnosis' and therefore cannot currently be acceptable as key regulatory endpoints. While this is clearly true, I (Daniel Leffler) argued that celiac serologies are direct manifestations of celiac disease activity and have the benefits of being non-invasive and widely used in clinical practice (unlike quantitative histology). For this reason, celiac serologies should be included in all clinical trials for both cohort stratification and as an excellent safety measure in phase IV trials.

There is good reason to believe that celiac disease is entering a new phase, moving away from the now outdated concepts of the adequacy of the gluten-free diet to appreciation of celiac disease of a burdensome and morbid condition with a high, unmet medical need. While hurdles remain, not the least of which include availability of patient-reported outcomes and responder definitions, this first GREAT meeting for celiac disease was notable for a remarkable degree of collegiality and shared vison among participants from all groups. Finally, there is buy in from patients, clinicians, industry and regulatory bodies that the status quo in celiac disease cannot be allowed to stand and that we have the tools we need to improve the lives of individuals with celiac disease. ■

The status quo in celiac disease cannot be allowed to stand.

These issues are all vexing but perhaps most relevant to patients and clinicians is the fact that despite the prevalence, morbidity, burden and overall highly unmet medical need, the field of celiac therapeutics has been nascent.

TREAT COMPLICATED HCV PATIENTS BEFORE

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Dr. Brown receives honoraria and institutional research support from Gilead, AbbVie and Janssen.

The recent transformation in our ability to eradicate chronic hepatitis C virus (HCV) infection with well-tolerated, potent interferon-free regimens has dramatically changed our management of HCV before and after liver transplantation. Treatment for cure on the liver transplantation waiting list to potentially decrease the need for transplantation or to eliminate the risk of recurrent disease in the allograft would be the ideal approach if feasible and risk-free for all. Indeed, the dramatic improvement in the efficacy and tolerability of the direct acting antiviral (DAA) agents now renders the goal of treatment for all patients, either before or after liver transplantation, a potential reality. However significant questions remain about the optimal timing of treatment in individual patient scenarios.

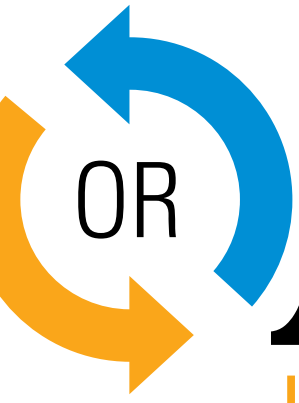
The pre-liver transplantation treatment strategies currently being employed include:

1. Treatment to achieve a sustained virologic response on the waiting list. This is most often utilized in patients with compensated cirrhosis, but now also in patients with other indications for liver transplantation (such as hepatocellular carcinoma) or in patients with mildly decompensated disease in whom stabilization without transplantation is a reasonable goal.

2. Treatment in the immediate pre-liver transplantation setting with the goal of liver transplantation during virologic suppression to prevent post-liver transplantation recurrence.

While trials with several direct acting antiviral combinations for patients with decompensated [Child Turcotte Pugh (CTP) class B or C] cirrhosis are ongoing or have been preliminarily reported, to date there remain limited published data, particularly in patients with Model for End-Stage Liver Disease (MELD) scores high enough (greater than 25) to be transplanted in many regions of the U.S.

Although the safety of these regimens appears to be superior to interferon-based therapies in patients with decompensated disease, the currently available safety datasets are small and there are ongoing concerns about the impact of moderately to severely impaired liver function on the metabolism of many of these agents. In addition, while there is great interest in the possibility of "recompensation" of liver function in the setting of sustained virologic response, the proportion of patients who will no longer require liver transplantation for long-term survival is unknown, as is which patients will achieve this resolution of symptoms. Finally, there is likely a group of patients



AFTER

LIVER TRANSPLANTATION?

for whom treatment on the waiting list with marginal improvement in liver function but ongoing indications for liver transplantation could put them at a disadvantage in terms of organ access. In these cases, the lowering of MELD scores and elimination of the potential use of HCV-seropositive donors could prolong time to transplantation and paradoxically increase waiting list mortality.

Post-liver transplantation HCV treatment has also been revolutionized with interferon-free therapy. With post-liver transplantation treatment trials in stable patients now consistently reporting sustained virologic response rates greater than 90 percent, perhaps higher than that achieved in patients with CTP class B and C disease on the liver transplantation waiting list, the relative benefits of pre-liver transplantation treatment may be less compelling in some cases. There are even now a significant number of reports of improvement in liver function as measured by MELD and CTP class in patients with recurrent advanced disease post-transplantation and/or severe forms of recurrence including fibrosing cholestatic HCV. However, while it would be theoretically desirable to treat as early post-liver transplantation as possible to minimize the risk of early severe recurrence, there are currently no data on the safety and efficacy of HCV treatment in immediate or very early post-liver transplantation (pre-emptive) setting. It remains unknown how high-dose immunosuppression, as well as possible treatment interruptions due to fluctuations in renal function and post-operative complications in the early post-operative period will impact response rates, and the impact of treatment at different post-liver transplantation intervals on graft survival has not been demonstrated.

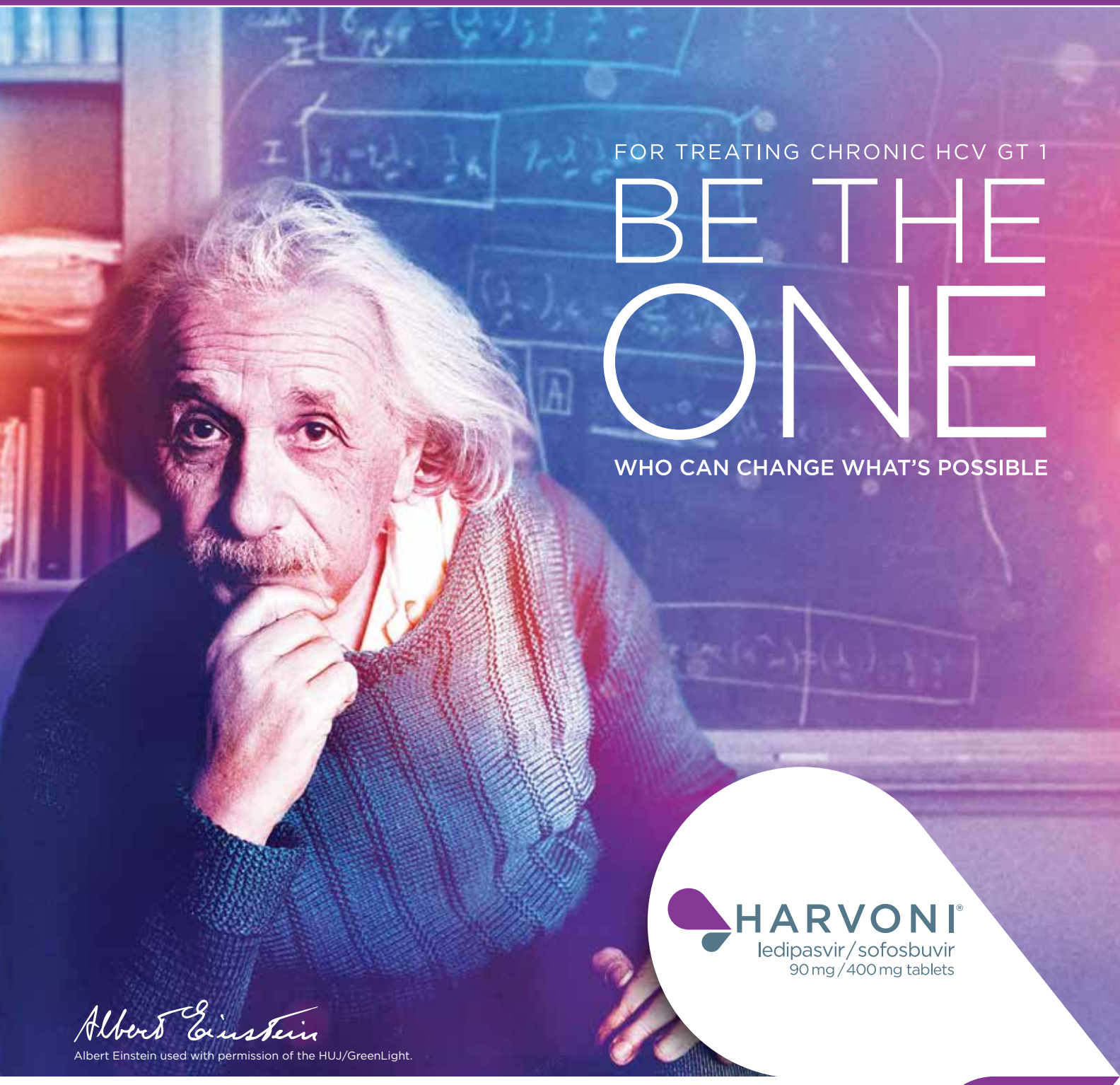
Given the balance of data currently available, we believe that the risks and benefits of HCV treatment should be discussed with all viremic patients on the liver transplantation waiting list, in conjunction with their transplantation center. Most patients with decompensated cirrhosis, particularly CTP class C, should likely have their treatment coordinated by a transplant hepatologist. In addition, given the uncertainty regarding the optimal regimen (efficacy of specific direct acting antiviral combinations, 12 or 24 weeks of treatment, and whether ribavirin is needed), and the need for safety data in these high-risk patients, we advocate for treatment in a clinical trial when possible. Additional considerations for individualized treatment recommendations in these complex patients include the importance of drug-drug interactions in both the pre- and post-transplantation settings, as well as comorbidities including renal dysfunction.

> HCV treatment in the setting of liver transplantation should remain individualized.

It is important to note that all current clinical data in patients with decompensated cirrhosis and post-liver transplantation have used direct acting antiviral therapy with ribavirin for 12 to 24 weeks. Currently, treatment should specifically be offered to patients on the liver transplantation waiting list with compensated CTP class A cirrhosis, or decompensated CTP B (and possibly C) cirrhosis with a reasonable expectation of the timing of transplantation (with living donation or MELD exception points). In addition, treatment could be considered in patients with mildly decompensated disease and relatively low MELD (less than 15) in whom the possibility of clinical improvement could provide an opportunity to avoid liver transplantation in the short term.

Conversely, we are currently waiting to treat post-liver transplantation in patients with severe hepatic impairment (CTP class C disease and high MELD), especially those with significant renal failure, as well as in those patients with more moderate MELD but strong indications for transplantation, such as severe complications of portal hypertension that are unlikely to completely resolve with treatment. For these patients, we believe that the risks of further limiting organ access with moderate lowering of MELD and/or eliminating the use of HCV seropositive donors outweigh the benefits given the high likelihood of cure in the post-liver transplantation period.

As HCV remains the leading indication for liver transplantation, data on the most effective HCV treatment strategies in patients with end-stage liver disease are urgently needed. In addition, given the current health-care financial pressures, it would be ideal to minimize the number of patients who require retreatment. While interferon-free therapies represent a tremendous advance in our ability to cure this previously difficult to treat population, given the limited data on safety in patients with severely decompensated cirrhosis, on the consequences of virologic failure, and on the impact of early viral eradication on post-liver transplantation liver function, we believe that HCV treatment in the setting of liver transplantation should remain individualized. ■



Albert Einstein used with permission of the HUJ/GreenLight.

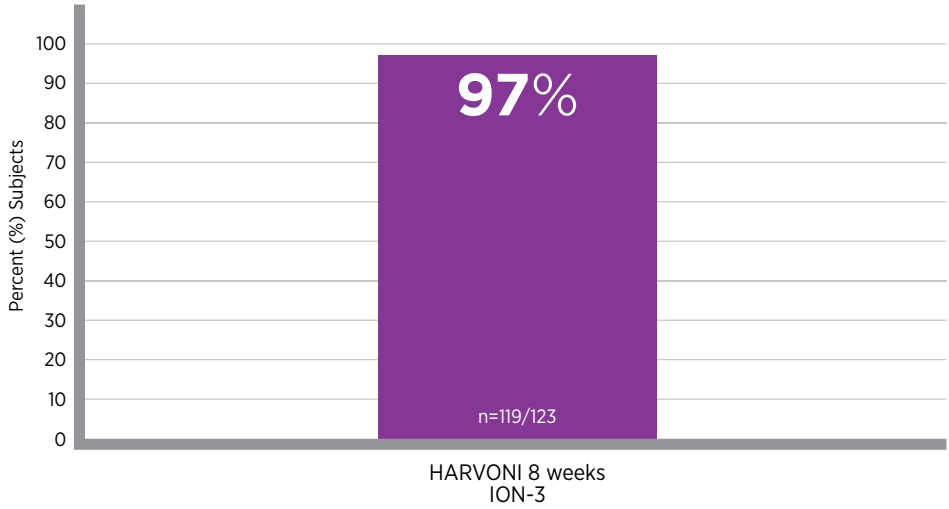
INDICATION

HARVONI is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

Please see Brief Summary of full Prescribing Information adjacent to this ad.

HARVONI is the only HCV treatment offering an 8-week course of therapy[1]

% SVR12 among treatment-naïve HCV GT 1 subjects without cirrhosis who had baseline HCV RNA <6 million IU/mL[1]



- Overall SVR12 was 94% (n=202/215) in subjects receiving HARVONI for 8 weeks[1,a]
- In treatment-naïve subjects taking HARVONI for 12 weeks, 96% (n=208/216) achieved SVR12 in the ION-3 trial and 99% (n=210/213) achieved SVR12 in the ION-1 trial[1,a]
- The recommended treatment duration for treatment-naïve patients is 12 weeks[1]
- HARVONI for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL[1]

Study Designs

ION-1[1]: a randomized, open-label trial evaluating HARVONI with or without ribavirin (RBV) in GT 1 treatment-naïve subjects (N=865) with or without cirrhosis. Subjects were randomized in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks, and stratified by presence or absence of cirrhosis and HCV genotype (1a vs 1b).

ION-3[1]: a randomized, open-label trial in GT 1 treatment-naïve subjects (N=647) without cirrhosis. Subjects were randomized in a 1:1:1 ratio to receive HARVONI for 8 weeks, HARVONI + RBV for 8 weeks, or HARVONI for 12 weeks, and stratified by HCV genotype (1a vs 1b).

[a]SVR12 was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the end of treatment.[1] Achieving SVR is considered a virologic cure.[2]

RBV was not shown to increase the response rates observed with HARVONI in ION-1 or ION-3. Therefore, the HARVONI + RBV arms are not presented.[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

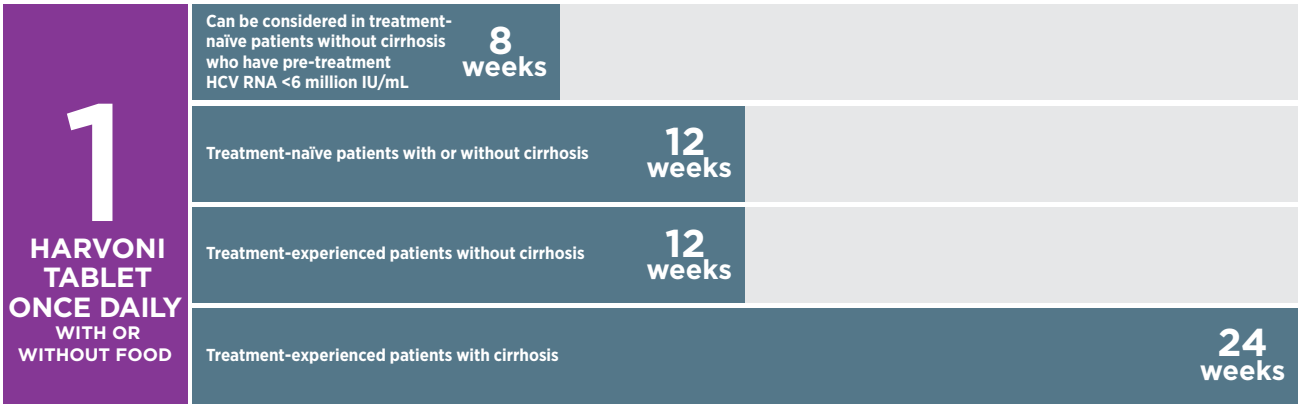
- **Risk of Reduced Therapeutic Effect of HARVONI Due to P-gp Inducers:** Rifampin and St. John's wort are not recommended for use with HARVONI as they may significantly decrease ledipasvir and sofosbuvir plasma concentrations.
- **Related Products Not Recommended:** HARVONI is not recommended for use with other products containing sofosbuvir (SOVALDI®).

ADVERSE REACTIONS

Most common (≥10%, all grades) adverse reactions were fatigue and headache.

HARVONI is the only once-daily single-tablet regimen for HCV GT 1 patients[1]

Recommended treatment duration[1]



- HARVONI is interferon- and RBV-free for GT 1 treatment-naïve and treatment-experienced patients with or without cirrhosis, regardless of GT 1a or 1b subtype[1]
- Each HARVONI tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir[1]
- Relapse rates are affected by baseline host and viral factors and differ between treatment durations for certain subgroups[1]
- No dose adjustments are required based on advanced age, mild or moderate renal impairment, or mild, moderate, or severe hepatic impairment. The safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis[1]
- No dose recommendations can be given for patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite[1]

IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS

- In addition to rifampin and St. John's wort, coadministration of HARVONI is also not recommended with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tipranavir/ritonavir. Such coadministration is expected to decrease the concentration of ledipasvir and sofosbuvir, reducing the therapeutic effect of HARVONI.
- Coadministration of HARVONI is not recommended with simeprevir due to increased concentrations of ledipasvir and simeprevir. Coadministration is also not recommended with rosuvastatin or co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of rosuvastatin and tenofovir, respectively.

Consult the full Prescribing Information for HARVONI for more information on potentially significant drug interactions, including clinical comments.

Please see Brief Summary of full Prescribing Information on the following pages.

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Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

INDICATIONS AND USAGE: HARVONI is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS:

Risk of Reduced Therapeutic Effect Due to P-gp Inducers: Concomitant use may significantly decrease ledipasvir and sofosbuvir concentrations and may lead to a reduced HARVONI effect. Use of HARVONI with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended.

Related Products Not Recommended: Use of HARVONI with products containing sofosbuvir (SOVALDI®) is not recommended.

ADVERSE REACTIONS:

The safety assessment of HARVONI was based on pooled data from three Phase 3 clinical trials in subjects with genotype 1 CHC with compensated liver disease (with and without cirrhosis) who received HARVONI for 8 (N=215), 12 (N=539) and 24 (N=326) weeks. Adverse events led to permanent treatment discontinuation in 0%, <1% and 1% of subjects receiving HARVONI for 8, 12 and 24 weeks, respectively.

Adverse Reactions (adverse events assessed as causally related by the investigator): The most common adverse reactions (≥10%; all grades) were fatigue and headache. Adverse reactions (all grades; majority Grade 1) observed in ≥5% of subjects by treatment duration were:

- *HARVONI for 8 weeks:* fatigue (16%); headache (11%); nausea (6%); diarrhea (4%); and insomnia (3%)
- *HARVONI for 12 weeks:* fatigue (13%); headache (14%); nausea (7%); diarrhea (3%); and insomnia (5%)
- *HARVONI for 24 weeks:* fatigue (18%); headache (17%); nausea (9%); diarrhea (7%); and insomnia (6%)

Direct comparison across trials should not be made due to differing trial designs.

Laboratory Abnormalities: *Bilirubin Elevations:* Bilirubin elevations of greater than 1.5x ULN were observed in 3%, <1% and 2% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. ***Lipase Elevations:*** Transient, asymptomatic lipase elevations of greater than 3x ULN were observed in <1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. ***Creatine Kinase:*** Creatine kinase was not assessed in Phase 3 trials of HARVONI. Isolated, asymptomatic creatine kinase elevations (Grade 3 or 4) have been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

DRUG INTERACTIONS:

Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir and sofosbuvir are substrates of P-gp and BCRP while the inactive sofosbuvir metabolite GS-331007 is not. P-gp inducers (e.g. rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect; use of HARVONI with P-gp inducers is not recommended.

Established and Potentially Significant Drug Interactions: The drug interactions described are based on studies conducted in healthy adults with either HARVONI, the components of HARVONI as individual agents, or are predicted drug interactions that may occur with HARVONI. This list includes potentially significant interactions but is not all inclusive. **An alteration in dose or regimen may be recommended for the following drugs when coadministered with HARVONI:**

- **Acid Reducing Agents:** Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease ledipasvir concentration.
  - *Antacids:* Separate HARVONI and antacid administration by 4 hours.
  - *H_2-receptor antagonists:* Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from HARVONI.
  - *Proton-pump inhibitors:* Doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.
- **Antiarrhythmics (digoxin):** Increased digoxin concentration. Monitor digoxin therapeutic concentration during coadministration with HARVONI.
- **Anticonvulsants (carbamazepine; phenytoin; phenobarbital; oxcarbazepine):** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- **Antimycobacterials (rifabutin; rifampin; rifapentine):** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- **HIV Antiretrovirals**
  - *Regimens containing tenofovir disoproxil fumarate (DF) and an HIV protease inhibitor/ritonavir (emtricitabine/tenofovir DF plus atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir):* The safety of increased tenofovir concentrations has not been established.

Brief Summary (cont.)

Consider alternative HCV or antiretroviral therapy. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.

- *Efavirenz/emtricitabine/tenofovir DF:* Monitor for tenofovir-associated adverse reactions. Refer to VIREAD, TRUVADA or ATRIPLA prescribing information for renal monitoring recommendations.
- *Elvitegravir/cobicistat/emtricitabine/tenofovir DF:* The safety of increased tenofovir concentrations has not been established. Coadministration is not recommended.
- *Tipranavir/ritonavir:* Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

- **HCV Products (simeprevir):** Increased ledipasvir and simeprevir concentrations. Coadministration is not recommended.
- **Herbal Supplements (St. John's wort):** Decreased ledipasvir and sofosbuvir concentrations. Coadministration is not recommended.
- **HMG-CoA Reductase Inhibitors (rosuvastatin):** Significant increase in rosuvastatin concentrations and risk of rosuvastatin associated myopathy, including rhabdomyolysis. Coadministration is not recommended.

Drugs without Clinically Significant Interactions with HARVONI: Based on drug interaction studies conducted with HARVONI or its components, no clinically significant drug interactions have been observed or are expected when used with the following drugs individually: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, tenofovir DF or verapamil.

Consult the full Prescribing Information prior to and during treatment with HARVONI for potential drug interactions; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS:

Pregnancy: HARVONI is Pregnancy Category B; there are no adequate and well-controlled studies in pregnant women. HARVONI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Studies in rats have demonstrated that ledipasvir and GS-331007 are secreted in milk but had no effect on nursing pups. It is not known if HARVONI and its metabolites are secreted in human breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HARVONI and any potential adverse effects on the nursing child from the drug or from the underlying maternal condition.

Pediatric Use: Safety and effectiveness of HARVONI have not been established in pediatric patients.

Geriatric Use: Clinical trials of HARVONI included 117 subjects aged 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of HARVONI is warranted in geriatric patients.

Renal Impairment: No dosage adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD.

Hepatic Impairment: No dosage adjustment of HARVONI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis.

References: 1. HARVONI US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. October 2014.
2. US Department of Health and Human Services, Center for Drug Evaluation and Research. Draft Guidance for Industry. Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. October 2013.

GILEAD

Classifieds

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QUALITY MEASURES in Gastroenterology

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Dr. Gellad serves on a clinical event adjudication committee for Merck.

In 2001, the Institute of Medicine published its landmark report entitled "*Crossing the Quality Chasm: A New Health System for the 21st Century*." While certainly not the beginning of the quality movement in health care, this report lit the fuse that led to an explosive growth of health-care quality programs over the next decade.

The metaphorical explosive at the end of this fuse was the Affordable Care Act (ACA), signed in 2010. This law marked a shift in quality programs from pay-for-reporting to pay-for-performance and ushered in the value-based health-care marketplace. The Department of Health and Human Services (HHS) has laid out ambitious goals for reforming health-care delivery through increased use of incentives to motivate higher-value care. For example, HHS has a goal to link 90 percent of all Medicare fee-for-service payments to quality or value by 2018.[1]

For our gastroenterology practices to thrive in this value-based marketplace, we need to understand the implications of current quality measures and anticipate the impact of future measures. This task is herculean given the number of programs underway in the public and private domains. Nonetheless, there are two key government programs that largely shape current discussions.

First is the Physician Quality Reporting System (PQRS). PQRS is a pay-for-reporting program that uses payment adjustments to promote reporting of quality information by eligible professionals, including non-physician providers, and group practices. Failure to participate in the program in 2015 will result in a negative 2 percent adjustment to the Medicare Part B Physician Fee Schedule in 2017. Measures in the PQRS program come from a variety of sources, including but not limited to GI specialty societies. Table 1 includes gastroenterology-specific measures and reporting options for those measures. The lowest threshold for entry is the disease specific measures groups, available for IBD and hepatitis C, in which the eligible professional needs to report on only 20 patients, a majority of which must be Medicare fee-for-service patients. Colorectal cancer screening metrics are reportable by claims or through a Qualified Clinical Data Registry (QCDR), although the reporting threshold is much greater at 50 percent of eligible patients.

IMAGE COURTESY OF THINKSTOCK.COM

WASHINGTON - U.S. President Barack Obama signs the Affordable Health Care for America Act during a ceremony with fellow Democrats in the East Room of the White House, March 23, 2010, in Washington, DC.

The second key program all GI providers should be aware of is the Value-Based Modifier Program (VBM). This program establishes differential payments to providers based on the quality and cost of care provided to Medicare beneficiaries. Quality measures will initially derive from the PQRS program. Costs will be determined using total per capita costs for attributed patients, with episode-of-care costs under development. Participating providers, meaning those who participate in PQRS in 2015, are eligible for up to a positive 4 percent incentive if they are

Table 1: Gastroenterology-Specific PQRS Measures

CLINICAL AREA	MEASURE TITLE	PQRS #	REPORTING OPTION(S)
HCV	Ribonucleic Acid (RNA) Testing Before Initiating Treatment	84	Measure Group
	HCV Genotype Testing Prior to Treatment	85	Measure Group
	Hepatitis C Virus (HCV) Ribonucleic Acid (RNA) Testing Between 4-12 Weeks After Initiation of Treatment	87	Measure Group
	Hepatitis A Vaccination	183	Measure Group
	Discussion and Shared Decision Making Surrounding Treatment Options	390	Measure Group; Registry
	Screening for Hepatocellular Carcinoma (HCC) in Patients with Hepatitis C Cirrhosis	401	Measure Group; Registry
IBD	Preventive Care: Corticosteroid Sparing Therapy	270	Measure Group; Registry
	Preventive Care: Corticosteroid Related Iatrogenic Injury – Bone Loss Assessment	271	Measure Group; Registry
	Testing for Latent Tuberculosis (TB) Before Initiating Anti-TNF Therapy	274	Measure Group; Registry
	Assessment of Hepatitis B Virus (HBV) Status Before Initiating Anti-TNF Therapy	275	Measure Group; Registry
CRC	Colorectal Cancer Screening	113	Claims; EHR; GPRO; Measure Group; Registry
	Colonoscopy Interval for Patients with a History of Adenomatous Polyps – Avoidance of Inappropriate Use	185	Claims; Registry
	Appropriate Follow-Up Interval for Normal Colonoscopy in Average Risk Patients	320	Claims; Registry
	Screening Colonoscopy Adenoma Detection Rate	343	Registry

high quality and low cost compared to peers. Non-participating providers risk up to a negative 4 percent payment adjustment in 2017, which is on top of the negative 2 percent reduction for PQRS alone. Of note, an additional VBM program for ambulatory surgical centers is also currently under development.

The PQRS and VBM programs shape the current quality environment, but I don't believe that the movement will end there. Where will the transformation take us? First, the widespread adoption of electronic health records (EHRs) will enable more sophisticated and real-time measures of health-care quality, including a movement away from process measures and toward clinically meaningful outcome measures. Development of these electronic measures may also speed the cycle of measure development and implementation, which is at least three years for most federal programs.[2] Secondly, private payors have begun and will most certainly continue to develop their own value programs, such as the physician tiering programs by United Health Care and Blue Cross Blue Shield. While the current quality measures in these programs are not aligned with PQRS measures, I believe that with increasing adoption of EHRs, there will be convergence of quality measures between public and private payors. Thirdly, the development of novel patient engagement strategies, including mobile health technology, will increase the patient voice in quality measurement. Understanding this voice, and creating mechanisms to respond to it, will become an increasingly important piece of quality improvement. Finally, the era of transparency in health-care delivery has arrived, and quality measurement will be at the forefront. CMS is mandated by the ACA to make information on physician performance publically available through the Physician Compare website. Private payors will not be far behind.

In summary, the quality measurement landscape continues to evolve, although one consistent theme has emerged, namely that measuring and reporting on quality has become an expectation for clinical practice. In the short term, with the expected 30 percent increase in Medicare enrollment over the next decade,[3] providers should make PQRS reporting a priority as this has become the centerpiece of the government's quality management program. In the longer term, developing an infrastructure for electronic quality reporting will be paramount. ■

For our gastroenterology practices to thrive in this value-based marketplace, we need to understand the implications of current quality measures and anticipate the impact of future measures.

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www.gastro.org/roadmap

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TREATMENT OF *H. PYLORI*

Is eradication really the best strategy?

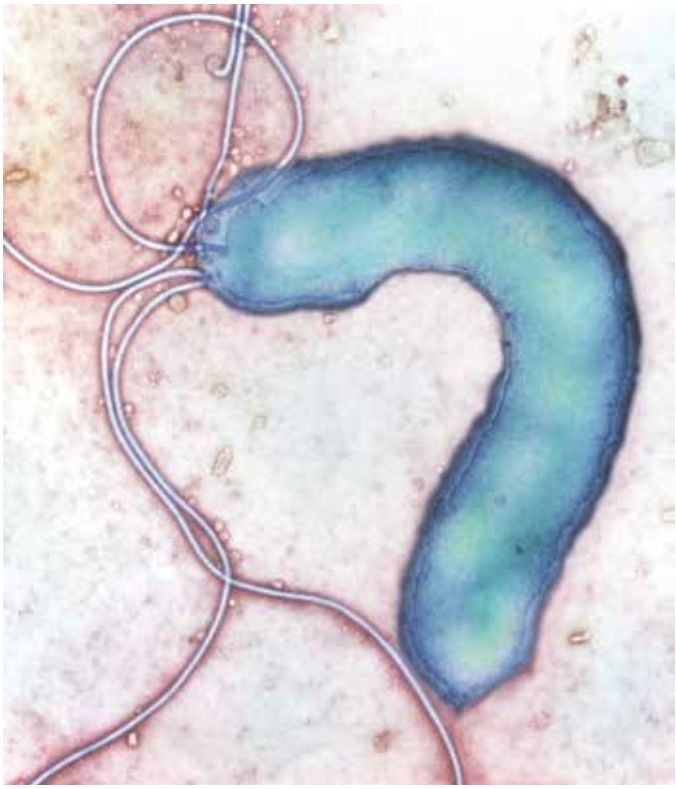
David Y. Graham, MD

Department of Medicine, Michael E. DeBakey VA Medical Center, and Baylor College of Medicine Houston, TX

Dr. Graham is a consultant for RedHill Biopharma regarding novel H. pylori therapies and has received research support for culture of H. pylori. He is a consultant for Otsuka Pharmaceuticals regarding diagnostic breath testing and for BioGaia in relation to probiotic therapy for H. pylori infection.

H. pylori is an infectious disease that I believe humans would be better off without. We have entered a new era. In 2013, the Japanese government approved population-wide *H. pylori* eradication. In 2014, WHO published a monograph on *H. pylori* eradication as a strategy of elimination of gastric cancer. Finally, in 2015, the Global Consensus on *H. pylori* gastritis published in *Gut* and recommended overall *H. pylori* eradication. Suggestions that *H. pylori* might provide a benefit have not withstood critical examination and are no longer an issue.

IMAGE COURTESY OF NIBSC / SCIENCE SOURCE



***Helicobacter pylori* bacterium. Colored transmission electron micrograph (TEM) of a single *Helicobacter pylori* bacterium.**

Worldwide, hundreds of millions of individuals are *H. pylori*-infected and most reside in regions already burdened with poverty and other major public health problems. While the goal to eradicate *H. pylori* is clear, the path to achieving that goal will need to be both population- and region-specific. I agree with the edict that all diagnosed *H. pylori* infections should be eradicated unless there are compelling reasons not to do so. We can all think of a few reasons (i.e., too old, too sick, etc).

Here, I discuss the problems of *H. pylori* eradication at the level of the patient and their physician. *H. pylori* is an infectious disease. It would be simple to cure (greater than 95 percent success) if one could reliably choose antimicrobials to which the infection is susceptible. Unlike other common infectious diseases, culture of *H. pylori* is generally unavailable and physicians must attempt to predict susceptibility using experience or by playing the odds. Clarithromycin susceptibility testing can be easily and reliably assessed using molecular methods on gastric biopsies or even from stools, but even that is rarely available. Experience relies on knowing what is successful in one's population. This knowledge, combined with the patient's medical history and pharmacy records, allows one to narrow the choices regarding which antibiotics to use.

Macrolides and fluoroquinolones suffer from cross resistance; prior use of a drug of these types (eg, azithromycin or ciprofloxacin) generally means the infection is resistant and should eliminate them from empiric use (i.e., cure rates with any triple therapy such as PPI, amoxicillin and clarithromycin, metronidazole, or a fluoroquinolone is 10 percent or less with resistance infections). Amoxicillin, tetracycline and metronidazole, when part of 14-day bismuth quadruple therapy, can be reused. It is important not to have false expectations based on published results (noting 85 percent success rates) as the overall result reflect the results of averaging a high success group with susceptible strains and very poor success with resistant strains. No patient achieves the reported 85 percent, but instead would fall into one of those two groups (i.e., under 10 or over 90 percent).

While the goal to eradicate *H. pylori* is clear, the path to achieving that goal will need to be both population- and region-specific.

If necessary to treat empirically, I suggest one know two equivalent first-line alternatives. I use concomitant therapy (PPI omeprazole 40 mg or equivalent, 500 mg clarithromycin, 500 mg metronidazole, and 1000 mg amoxicillin, b.i.d. for 14 days) or bismuth quadruple therapy (PPI, omeprazole 40 mg or equivalent b.i.d., 500 mg metronidazole t.i.d., 500 mg tetracycline q.i.d. and bismuth such as Pepto Bismol 2 tablets q.i.d. for 14 days).

Concomitant therapy is undermined only by dual clarithromycin-metronidazole resistance and is generally well tolerated. Tetracycline may be difficult to obtain; it is available from Canada. Our experience is that doxycycline is not an adequate substitute. The commercial product, Pylera, is packaged for 10-day therapy and the PPI must be prescribed separately. In the U.S., Pylera is expensive, often $400 for 10 days. We prescribe 14-day therapy and it often costs $600 or more. Generic therapy costs about $40 at Walmart.

Adherence to the prescribed regimen is a problem with all *H. pylori* therapies and it is worth the time and effort to discuss the importance of finishing the prescription and the expected side effects with the patient. Bismuth quadruple therapy is especially useful in the presence of penicillin allergy or to treat patients who have failed another regimen. Sequential therapy and triple therapy (i.e., PrevPac or an equivalent) are still widely used but are obsolete for empiric use. Concomitant and sequential therapy contain the same drugs but concomitant will always be equal or superior to sequential therapy. I believe that all patients should have a test of cure (i.e., urea breath test or stool antigen test) as only cured patients benefit from therapy. In addition, this information provides data regarding individual therapies in your patient population (i.e, what works, and what no longer works).

For suggestions regarding the difficult patient (i.e., prior treatment failure, drug allergies, etc.) or details regarding above, see my recent reviews in *Gastroenterology* and *Clinical Gastroenterology and Hepatology*. ■

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New AGA Institute President Will Guide Organization in Implementing Strategic Plan

Camilleri

Michael Camilleri, MD, MPhil, MRCP, FACP, AGAF, of the Mayo Clinic in Rochester, MN, began his term as the 110th president of AGA Institute immediately following Digestive Disease Week® (DDW) 2015.

Dr. Camilleri's longtime commitment to mentoring and leadership will translate into his new role at AGA, where he will work to ensure that the organization is a home away from one's own institution or practice — providing gastroenterologists with career support, research funding, a voice on Capitol Hill, practice resources and opportunities for educational advancement.

"I'm excited to embark on this leadership position and look forward to helping AGA members navigate the clinical landscape, from trainees to seasoned physicians," said Dr. Camilleri.

As president, Dr. Camilleri will guide AGA in implementing the 2015–2020: AGA Strategic Plan, which is focused on advancing the science and practice of gastroenterology through three fundamental areas: practice and quality, research and innovation, and education and training, all supported by strong advocacy efforts, prestigious publications and organizational support. These key initiatives will include a focus on advocating for fair reimbursement, working effectively with FDA and industry, and further developing AGA's relations with patients.

"Together with the AGA Governing Board and leadership cabinet, I will work tirelessly to implement the new AGA Strategic Plan, with the goal of continuing the advancement of education, research and innovation in the GI community," added Dr. Camilleri.

Dr. Camilleri has served AGA in many capacities throughout the past 25 years, particularly shining in the editorial realm where he has helped to establish and advance AGA's publications. Among his many contributions, he was the creator and first editor of AGA's flagship clinical journal, *Clinical Gastroenterology and Hepatology*, the associate editor of *Gastroenterology* from 1996 to 2001 and the editor of *AGA Perspectives* from 2007 to 2010. He also served as chair of the AGA Institute Council Neurogastroenterology Section, after which he received AGA's 2015 Neurogastroenterology Section Research Mentor award.

To learn more about Dr. Camilleri, read the *Gastroenterology* article detailing his early life, academic background, practice history and awards at AGA and beyond.

In 1977, after attending the University of Malta Medical School and completing two years of residency at St. Luke's Hospital in Malta, where he grew up, Dr. Camilleri attended the Hammersmith Hospital Royal Postgraduate School of Medicine in London, for both research and clinical training in internal medicine and gastroenterology. He also received a master's degree in physiology and medicine at the University of London and became a member of the Royal College of Physicians.

In 1983, following his work in London, Dr. Camilleri took a research fellow position in the division of gastroenterology and hepatology at Mayo Clinic, where he still works today. Although he briefly left Mayo to serve as deputy director in the Department of Medicine in Malta for two years, Dr. Camilleri returned to Mayo Clinic in 1985. Currently he is the Atherton and Winifred W. Bean professor of medicine, physiology and pharmacology, and the executive dean of development at Mayo Clinic, where he specializes in gastrointestinal motility.

VIEW OUR STRATEGIC PLAN ONLINE AT WWW.GASTRO.ORG/ABOUT.

Dr. Camilleri and his wife Josephine, who have been married for nearly 40 years, have four children: Michael, Christopher, Alex and Hannah. ■

Highlights from the 2015 AGA Tech Summit


Kochman

This past March, the AGA Center for GI Innovation and Technology held the sixth annual AGA Tech Summit, one of our many initiatives to advance the practice of gastroenterology by supporting innovation in the field of gastroenterology. The summit brings together physicians, medical device companies, regulatory groups and venture capitalists to identify unmet needs in gastroenterology and highlights promising new technologies.

This year's meeting provided a look at recent med-tech successes and failures, the future of 3D printing (hint: made-to-order livers), the unmet need for obesity devices, how to make complicated purchasing decisions, and much more. Experts in the field provided attendees with vital information on what it takes to obtain approval, adoption, coverage and reimbursement in today's health-care environment.

Access full coverage of the AGA Tech Summit.

To review the most practical information presented at this year's summit. Head over to **www.gihepnews.com** and click "AGA Meetings." Be sure to check out the video interviews to hear from the experts paving the way in technology and innovation.

The AGA Center for GI Innovation and Technology is committed to keeping our field vibrant, and we will continue to update you and keep you informed on how new technologies will impact your practice and improve patient care.

Sincerely,

Michael Kochman, MD, AGAF, chair,
AGA Center for GI Innovation and Technology

P.S. Save the date: the 2016 AGA Tech Summit will take place March 31 and April 1, 2016, in Boston, MA.

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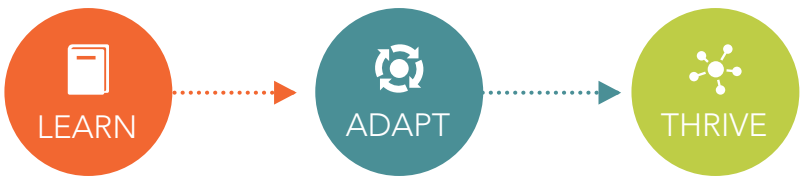

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